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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/366,083	12/29/1994	JOEL L. POMERANTZ	APBI-P01-022	6870

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EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/366,083	POMERANTZ ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003 and 08 April 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *99-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 99, 101-114, and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new rejection necessitated by applicant's addition of claims filed 4/8/03.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains,

each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

These are genus claims. The specification fails to disclose even one embodiment that definitively meets the claim limitations because the specification does not teach that any one embodiment is definitely not present in nature. The specification also fails to teach how one of skill in the art would know that a particular combination of nucleic acid binding domains or spacing or order are definitely not found encoded in a natural gene. There is no description of what combinations of nucleic acid binding domains definitely do not exist in nature. The general knowledge in the art concerning known genes and gene mutations does not provide any indication of the excluded structures of nucleic acids of natural genes that have not been identified or sequenced yet, but which are still excluded by the claim limitations. The nature of different genes in the art is that they tend to vary unpredictably and thus, unless the nucleotide sequence of the different genes are empirically determined, they are not known and not predictable. Natural

mutations that can change the spacing or order of DNA binding domains of a wild type protein are unpredictable. The present and foreseeable state of the art is that the structure of one or more known genes does not predict the specific structures of one or more other genes that are presently unknown. The common structural attributes of the genus are not described. One of skill in the art would conclude that applicant was not in possession of the claimed genus, especially because there is no description of even one member of the claimed genus that definitively meets the claim limitations because it was not shown that the nucleic acid was not present in nature, and thus, the description of the claimed invention is insufficient to support the claims.

Claims 99, 101-114, and 118 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection necessitated by applicant's addition of claims filed 4/8/03.

The claimed invention is drawn to a nucleic acid and its use, the nucleic acid encoding a chimeric protein which binds a nucleic acid comprising a composite binding site, wherein the chimeric protein comprises two nucleic acid binding domains, each of which binds a sequence which is a portion of the composite binding site, and wherein the two nucleic acid binding domains do not occur in the same protein in nature, do not occur in the same protein in nature in the order in which they are present in the chimeric protein, or do not occur in nature with the same spacing that is present in the chimeric protein.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claim. The most relevant Wands factors for evaluating the enablement of the instant rejection are discussed below.

The nature of the invention is complex because the exclusion conditions that form a limitation of the claimed nucleic acids and methods is complex, that such a combination of nucleic acid binding domains is not present in nature, nature

being hugely complex. There are a limitless number of genes encoding different proteins in nature, especially including natural recombinants of those genes which resulted from a fusion between genes encoding different proteins, including different DNA binding proteins, which may result in natural chimeric nucleic acids as claimed (excluding the not present in nature part of the claim limitations). An example of such natural fusions that occurs in nature are chromosomal breakpoint mutations, some of which involve DNA binding proteins.

The nucleic acids which meet the claimed limitations are highly unpredictable because for any given nucleic acid, all of the natural nucleic acids that exist in the natural world must be empirically determined and their sequences searched in order to determine whether the particular nucleic acid is encompassed by the claims or not. Without doing this, it is impossible to predict for any given combination of nucleic acid binding domains in a chimeric protein encoded by a nucleic acid, whether the nucleic acid meets all of the claim limitations, including the exclusions.

The amount of guidance is slight because both the art and the specification fail to teach even a small fraction of all possible sequences that any given nucleic acid must be compared

to in order to determine whether that nucleic acid exists in nature or not.

Neither the art nor the specification teaches a working example of the claimed invention because neither the art nor the specification teaches a nucleic acid that definitively meets the claim limitations, that the combination of nucleic acid binding domains does not exist in nature.

In order to practice the claimed invention, one skilled in the art would have to envision an embodiment of the claimed invention, make it, test it in order to see whether it is functional in binding a composite DNA binding site, and if it does, then one skilled in the art would have to determine the nucleotide sequence of all genes that exist in nature, including mutant genes, and then compare the functional nucleic acid with all natural gene sequences in order to determine whether or not the nucleic acid is present in nature or not, and if it is not present in nature, then it is one functional embodiment that meets the claim limitations, out of the broad scope as claimed. This would require an absolutely enormous amount of experimentation because the nucleotide sequences of all natural genes, including all natural gene mutations would have to be determined in order to determine whether any particular nucleic acid meets the claim limitations. This amount of

experimentation could not be accomplished in less than an infinite amount of time to practice even only one embodiment, which would be considered to be undue to practice the invention as broadly claimed.

Claim Rejections - 35 USC § 102

Claims 99-104 and 106-119 are rejected under 35 U.S.C. 102(e) as being anticipated by Barbas et al (U.S. Patent No. 6,242,568). This is a new rejection necessitated by applicant's addition of claims filed 4/8/03. Applicants' arguments filed 4/8/03 have been fully considered but they are not deemed to be persuasive.

Barbas et al teach a nucleic acid encoding two or more heterologous zinc finger modules that specifically bind (with higher affinity) to a specific cellular nucleotide sequence (made from the specific binding sites of the zinc finger modules) and which, when brought into contact with the cellular nucleotide sequence, modulates the transcription from the cellular nucleotide sequence in the cell (columns 3-4; 26-28; throughout the reference and claims). Examples of known zinc finger-nucleotide binding proteins that can be truncated, expanded, and/or mutagenized according to the present invention in order to inhibit the function of a cellular sequence

containing a zinc finger-nucleotide binding motif includes TFIIIA and zif268. These nucleic acid binding motifs can separated by at least one amino acid (column 29). Others are known in the art (column 7). For obtaining zinc finger derived DNA binding polypeptides, the synthesis of DNA sequences is frequently the method of choice when the entire sequence of amino acid residues of the desired polypeptide product is known (column 9). This reference teaches placement of the nucleic acid encoding the proteins containing the chimeric zinc finger domains into vectors for expression in eukaryotic cells, under the control of a promoter sequence (columns 13 and 21). The vector in combination with a cell containing the specific cellular nucleotide sequence used in the method for modulating transcription, reads on a kit comprising the vector and a gene operably linked to a composite binding site to which the chimeric transcription factor binds. Barbas et al also teach that the zinc fingers may be modified to recognize a different sequence, and fused to other proteins which are capable of forming heterodimers and contain dimerization domains. Activation domains may also be incorporated to produce activators of transcription, which then allow for specific activation or repression of transcription (columns 27-28). A

particular example of this type of construct is taught (column 29).

Response to Arguments

The applicant argues that Barbas et al is not prior art because the effective 102(e) date is December 30, 1996 (as published on the first page) and that the present application was filed more than two years prior to this date (on December 29, 1994). This argument is not persuasive because Barbas et al (U.S. Patent No. 6,242,568) is a national stage entry of PCT/US95/00829 (which is a US case), which is a CIP of application no. 08/312,604, filed on September 28, 1994, which is a CIP of application no. 08/183,119, filed on January 18, 1994. Barbas et al is entitled to the benefit of the earlier filing dates, including the filing date of January 18, 1994, because the material relied upon in Barbas et al is fully supported by both earlier applications and the U.S. cases are in an unbroken chain of copending cases. Therefore, Barbas et al is accorded the priority date of January 18, 1994, and thus qualifies as art under 35 USC 102(e).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be

retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

November 17, 2003